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Case Report

Orthostatic hypertension: Recognizing an underappreciated clinical condition

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ABSTRACT

Orthostatic hypertension refers to an increase in the blood pressure upon assuming an upright posture. This clinical condition has been understudied and is often underappreciated in clinical practice probably because of its unfamiliarity to many clinicians including subspecialists. We report a case of severely symptomatic orthostatic hypertension in a Caucasian female, which was likely secondary to an autonomic dysfunction caused by an underlying vascular adrenergic hypersensitivity and possibly also due to uncontrolled diabetes mellitus (causing baroreflex dysfunction associated with excessive sympathetic stimulation). The case work-up also illustrates a schematic diagnostic and management approach to this rarely encountered clinical entity.

1. Case presentation

A 58-year-old Caucasian female presented to the emergency room with complaints of an intense, diffuse, throbbing headache, without radiation, which worsened upon sitting or assuming a standing position and was partially relieved while lying down. She had been well until a few weeks earlier when she noticed similar but milder episodes of intermittent headache and transient blurry vision. She also reported occasional palpitations. Her review of systems was otherwise negative. Past medical history was significant for hypertension and poorly controlled type 2 diabetes mellitus (DM), both diagnosed about over 10 years ago. Her medications included glipizide, metformin, and hydrochlorothiazide. She reported poor compliance with her medications and did not have a primary care follow-up for a long time. There was no family history of migraines or cluster headaches. Her initial physical examination was remarkable for an elevated blood pressure of 196/94 mmHg supine, 208/98 mmHg sitting and 236/118 mmHg standing, and for a heart rate of 85, 88 and 96 beats per minute, respectively. A few subsequent manual blood pressure measurements obtained in both arms were consistent with orthostatic increase in the blood pressure. Fundoscopic examination revealed mild (Grade 1) arteriolar narrowing. The rest of the systemic examination was largely unremarkable. She received intravenous labetalol and morphine in the emergency room and reported slight relief in her headache symptoms. The repeat blood pressure was 178/90 mmHg (supine) and 204/96 mmHg (sitting). Routine laboratory studies including hemogram, basic metabolic panel and liver function tests were unremarkable except random serum glucose level of 190 mg/dL and glomerular filtration rate of 58 mL/min/1.73 m^2, suggesting grade-3 chronic kidney disease. Chest X-ray and electrocardiogram were largely

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unremarkable. Computerized tomographic (CT) scan of the head and magnetic resonance imaging (MRI) of the head and neck at the time of admission were unremarkable. In lieu of her labile hemodynamics, she was subsequently admitted to the intensive care unit for closer monitoring. During her stay, she was continued on her home dose of hydrochlorothiazide and was initiated on other oral antihypertensive medications including lisinopril, metoprolol and amlodipine, which were gradually titrated to the optimal dosing regimen over the course of two days (and the IV labetalol was gradually stopped); however, the blood pressure control remained poor despite four antihypertensive drugs and patient continued to experience significant orthostatic fluctuations (rise) of her blood pressure associated with symptoms.

Further diagnostic work-up revealed a normal thyroid function profile and serum cortisol levels. HbA1c was 11%. Transthoracic echocardiogram (TTE) was unremarkable except evidence of mild mitral regurgitation and left ventricular hypertrophy. Urinary 24-hour catecholamine levels were obtained as a part of the work-up for resistant hypertension, which returned within the normal reference range: norepinephrine, 60 μg; epinephrine, 3 μg; normetanephrine, 284 μg; and metanephrine, 124 μg. The plasma catecholamine levels were also within the normal range and demonstrated an appropriate increase with postural change: With the patient after rest for 30 min in supine position and after standing time of 5 and 10 min, norepinephrine levels were 0.78, 1.39, and 1.37 nmol/L (normal at rest, 0.7–3.9 nmol/L), respectively, and epinephrine levels were 84, 89, and 56 pmol/L (normal at rest, <270 pmol/L). The 24-hour urinary levels of 5-hydroxyindoleacetic acid (5-HIAA) were normal (5 mg). Plasma aldosterone level, plasma renin activity and aldosterone to renin ratio were normal at supine resting position (4 ng/dL, 0.8 ng/mL/h and 5 ng/dL per ng/(mL–h), respectively). Magnetic resonance imaging/angiography (MRI/A) of the abdomen performed to rule out a renovascular cause of resistant hypertension showed evidence of only a small simple right renal cyst. A cold pressor test while supine revealed a moderate increase in the both systolic and diastolic blood pressure: her blood pressure increased from 162/84 (baseline) to 188/102 and 180/96 mm Hg at 1 and 2 min, respectively, of immersing hand in ice cold water. Minimally invasive hemodynamic monitoring done through a Flo Trac sensor revealed marked postural change in her blood pressure: 146/90 (supine), 170/98 (sitting) and 178/102 mmHg (standing). This was respectively associated with changes in cardiac output (5.8, 6.2 and 5.9 L/min); heart rate (84, 88 and 92/min) and systemic vascular resistance (SVR) (1428, 1584 and 1704 dynes/cm^5). The results of hemodynamic monitoring suggested a significant contribution by the primarily increased SVR toward orthostatic hypertension rather than a response to transient reduction in cardiac output. It also suggested exquisite alpha-adrenergic receptor hypersensitivity.

She was thereafter started on low dose clonidine with the aim of offering a central sympatholytic effect: it caused significant lowering of blood pressure to the range of 130–160/80–100 mm Hg with persistent but less severe orthostatic rise in her blood pressure ranging from about 12 to 20 mm Hg. She also reported moderate relief in her headache. Prazosin was later added to the therapeutic regimen, which caused marked improvement in both headache and blood pressure variations. She was offered a referral for pharmacological autonomic nervous function testing for cardiovascular system, which was, however, declined by the patient, given her significant clinical response to the treatment regimen.

She was discharged after 48 h of further monitoring; her blood pressures largely remained stable (ranging 130–146/70–90 mmHg) with minimal orthostatic variations in blood pressure ranging 10–15 mmHg. She was largely asymptomatic at the time of discharge.

2. Discussion

Orthostatic hypertension is an underappreciated and understudied clinical phenomenon and has no standard definition yet, but an operational definition based upon previous studies refers to it as an increase in systolic blood pressure of 20 mmHg when changing position from supine to standing.[1] Clinically symptomatic cases of orthostatic hypertension are probably rarely encountered. It is very important for the clinicians, especially emergency room physicians and cardiologists, to correctly recognize this entity. A variety of clinical conditions, which may be associated with this entity, include essential hypertension (mostly in elderly patients with significant diurnal variation of blood pressure), pheochromocytoma, type 2 DM, nephroptosis, medullary vascular compression and dysautonomia/autonomic dysfunction (mast cell activation disorder, postural tachycardia syndrome, baroreflex failure).[1–6] It has been associated with increased incidence of silent central nervous system ischemia and neuropathy in diabetes mellitus.[1,7] There has been no standard consensus in the diagnostic work-up and management of orthostatic hypertension. The information available from the previous studies on this subject suggests that the work-up should essentially include ruling out baroreflex failure and/or a search for surgically correctable causes of hypertension (like pheochromocytoma, carcinoid syndrome, medullary vascular hyperplasia etc.) should be undertaken.[1,8,9] This would include a battery of endocrinological and autonomic function testing as mentioned in our case. Currently, there is no sufficient data to suggest expensive or invasive testing for patients who are either normotensive or essentially hypertensive who also have asymptomatic orthostatic hypertension. The patient in our case developed orthostatic hypertension probably due to multiple factors, most likely due to autonomic dysfunction caused by an underlying vascular adrenergic hypersensitivity[8] and also possibly due to uncontrolled DM (causing diabetic autonomic neuropathy and baroreflex dysfunction associated with likely excessive sympathetic stimulation).[3] It may often be difficult to point out other clinical factors, which may have potentially contributed to the patient's presentation, and one could argue that chronic kidney disease and essential hypertension may also have played a role as well. Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) found the prevalence of orthostatic hypertension to be about 15% in their diabetic population.[10] Alpha antagonists and central sympatholytics may offer a promising clinical response, as in our patient. A recent open-label multicentric trial showed significant beneficial effects of doxazosin on orthostatic blood

pressure fluctuations in patients with orthostatic hypertension. The same study also concluded that doxazosin may prevent target organ damage in patients with orthostatic hypertension.[11]

The true incidence of orthostatic hypertension and its related complications remains unclear. Although orthostatic hypotension is commonly encountered and well known in patients with DM, the occurrence of orthostatic hypertension in long standing DM is often poorly recognized and treated by clinicians. There is little written on this subject in the medical literature; therefore, it is not surprising that this clinical entity is not well known to many primary care physicians and even specialists. Clearly, orthostatic hypertension represents an aspect of hypertension that is poorly understood and is in need of focused basic science and clinical inquiry. At the same time, a consensus should be reached regarding the diagnostic criteria and clinical management.

Conflicts of interest

All authors have none to declare.

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